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Ru-Catalyzed Intermolecular [3+2+1] Cycloaddition of α,*β*-Unsaturated Ketones with Silylacetylenes and Carbon Monoxide Leading to α-Pyrones

Takahide Fukuyama,* Yuki Higashibeppu, Ryo Yamaura, and Ilhyong Ryu*

Department of Chemistry, Graduate School of Science, Osaka Prefecture University,
Sakai, Osaka 599-8531, Japan

ryu@c.s.osakafu-u.ac.jp

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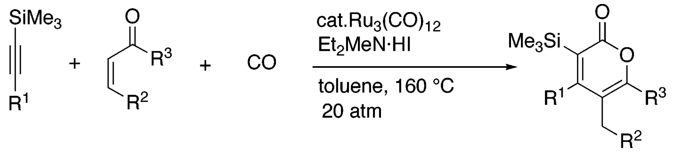
ABSTRACT



Ruthenium catalyzes a carbonylative [3+2+1] cycloaddition, using silylacetylenes, α,*β*-unsaturated ketones, and CO as the starting materials, providing the new method for the synthesis of tetrasubstituted α-pyrones. In this reaction, the carbonyl group and α-carbon of vinyl ketones are incorporated as a three-atom assembling unit.

α-Pyrones are useful as intermediates in the synthesis of a variety of important hetero- and carbocyclic molecules and can be found in numerous biologically active natural products as substructures.[1] Transition-metal-catalyzed cycloaddition, using carbon monoxide as a one-carbon unit, is one of the most powerful tools available for the construction of various carbonyl-containing cyclic and heterocyclic compounds,[2] however, analogous approaches leading to α-pyrones are scarce.[3,4] A few catalytic systems for the synthesis of α-pyrones based on the carbonylation have been developed. These include the carbonylation of cyclopropenyl esters or ketones,[3a] 2-iodoallyl-1,3-dicarbonyl compounds,[3b] and propargyl halides or propargyl alcohol.[3c] In these methods, however, only a limited range of substrates can be tolerated. We recently reported on the ruthenium-catalyzed [2+2+1+1]-type cycloaddition of alkynes, electron-deficient alkenes, and two molecules of CO, to give hydroquinones in good yields (Scheme 1, first equation).[5] During the course of our investigation, when silylacetylenes were used as an alkyne, we found that no such cycloaddition took place but α-pyrones were formed as the major products. Herein, we report on

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(3) (a) Cho, S. H.; Liebeskind, L. S. *J. Org. Chem.* **1987**, *52*, 2631. (b) Shimoyama, I.; Zhang, Y.; Wu, G.; Negishi, E. *Tetrahedron Lett.* **1990**, *31*, 2841. (c) Rosas, N.; Salmon, M.; Sharma, P.; Alvarez, C.; Ramirez, R.; Garcia, J.-L.; Arzoumanian, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1493.

(4) (a) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713. (b) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770. (c) Kotora, M.; Ishikawa, M.; Tsai, F.-Y. Takahashi, T. *Tetrahedron* **1999**, *55*, 4969. (d) Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Chem. Commun.* **2000**, 1987. (e) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936. (f) Cherry, K.; Parrain, J.-K.; Thibonnet, J.; Duchêne, A.; Abarbri, M. *J. Org. Chem.* **2005**, *70*, 6669. For [2+2+2] cycloaddition using carbon dioxide, see: (g) Tsuda, T.; Morikawa, S.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 3140. (h) Tsuda, T.; Morikawa, S.; Hasegawa, N.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2978. (i) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188.

(5) (a) Fukuyama, T.; Yamaura, R.; Higashibeppu, Y.; Okamura, T.; Ryu, I.; Kondo, T.; Mitsudo, T. *Org. Lett.* **2005**, *7*, 5781. For earlier work, see: (b) Suzuki, N.; Kondo, T.; Mitsudo, T. *Organometallics* **1998**, *17*, 766.

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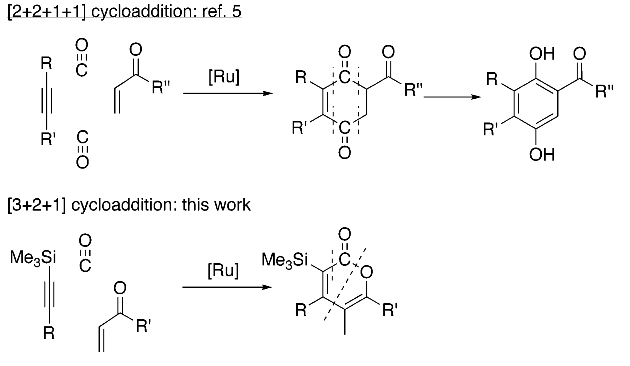
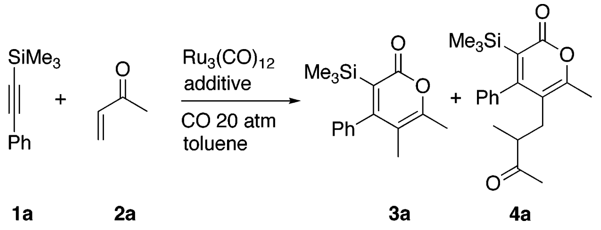
Scheme 1. Cycloaddition Reactions Leading to Hydroquinones and α-Pyrones Using Alkynes, Alkenes, and CO



the novel synthesis of α-pyrones by the $Ru_3(CO)_{12}$-catalyzed carbonylative [3+2+1] cycloaddition of vinyl ketones, silylacetylenes, and CO, in which vinyl ketones were incorporated as a three-atom assembling unit (Scheme 1, second equation).[6]

When the reaction of 1-(trimethylsilyl)-2-phenylacetylene (**1a**) with methyl vinyl ketone (**2a**, 3 equiv) under pressurized CO (20 atm) was carried out in the presence of a catalytic amount of $Ru_3(CO)_{12}$ at 140 °C for 20 h, a [3+2+1] cycloaddition reaction took place to give the α-pyrone **3a** in 20% yield (Table 1, entry 1). A significant amount of unreacted **1a** remained, and ^{1}H NMR and GC-MS analyses showed that neither the other regioisomers of **3a** nor hydroquinone was formed. Regiochemistry of the cycloaddition product **3a** was confirmed by an NMR analysis of the desilylation product.[4b,7] When the reaction was carried out in the presence of H_2O, the yield of **3a** was slighty improved (entry 2). In this case, 2-phenylvinylsilane, a reduced product, was also formed. The addition of NEt_3 led

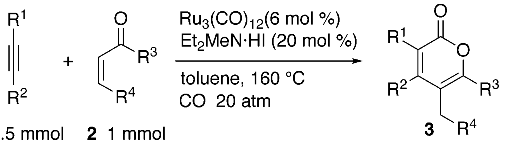
Table 1. Optimization of the $Ru_3(CO)_{12}$-Catalyzed [3+2+1] Cycloaddition of Methyl Vinyl Ketone, Trimethylsilyl Phenylacetylene, and CO

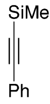
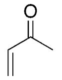
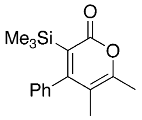
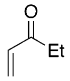
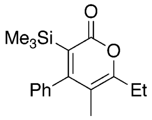
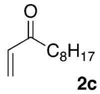
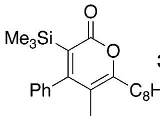
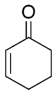
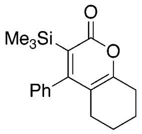
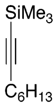
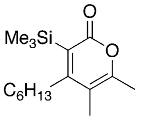
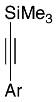
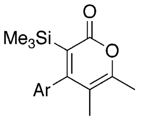
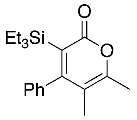
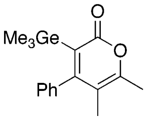


entry	conditions[a]	additive	yield[b] 3a	yield[b] 4a
1	140 °C, 20 h	none	20%	–
2	140 °C, 20 h	H_2O[c]	24%[d]	–
3	140 °C, 20 h	NEt_3	30%	–
4	140 °C, 20 h	TsOH	trace	–
5	140 °C, 20 h	$Et_2MeN{\cdot}HI$	40%	15%
6	160 °C, 8 h	$Et_2MeN{\cdot}HI$	52%	7%

[a] Reaction conditions: **1a** (0.5 mmol), $Ru_3(CO)_{12}$ (6 mol %), additive (20 mol %), toluene (2 mL), **2a** (1.5 mmol (1.0 mmol for entry 6)). [b] Isolated yield by flash chromatography on SiO_2. [c] 1.8 equiv. [d] 2-Phenylvinylsilane was formed.

Table 2. $Ru_3(CO)_{12}$-Catalyzed [3+2+1] Cycloaddition of Vinyl Ketones, Silylacetylenes, and Carbon Monoxide[a]



entry	1	2	3 yield[b]
1	 **1a**	 **2a**	 **3a** 52%
2	**1a**	 **2b**	 **3b** 57%
3	**1a**	 **2c**	 **3c** 55%
4[c]	**1a**	 **2d**	 **3d** 37%
5[c]	 **1b**	**2a**	 **3e** 15%
6	 **1c** p-MeOC$_6$H$_4$	**2a**	 **3f** 66%
7	**1d** p-FC$_6$H$_4$	**2a**	**3g** 57%
8	**1e** o-MeC$_6$H$_4$	**2a**	**3h** 59%
9	**1f** 1-naphtyl	**2a**	**3i** 54%
10	**1g** 2-naphtyl	**2a**	**3j** 51%
11	 **1h**	**2a**	 **3k** 29%
12	 **1i**	**2a**	 **3l** 15%

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), $Ru_3(CO)_{12}$ (6 mol %), $Et_2MeN{\cdot}HI$ (20 mol %), toluene (2 mL), 160 °C, 8 h. [b] Isolated yield by flash chromatography on SiO_2. [c] 20 h.

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[6] $Ru_3(CO)_{12}$-catalyzed carbonylative [2+2+1] cycloaddition using ketones or aldehydes as two-assembling units, see: (a) Chatani, N.; Morimoto, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 5335. (b) Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 7160. (c) Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663.

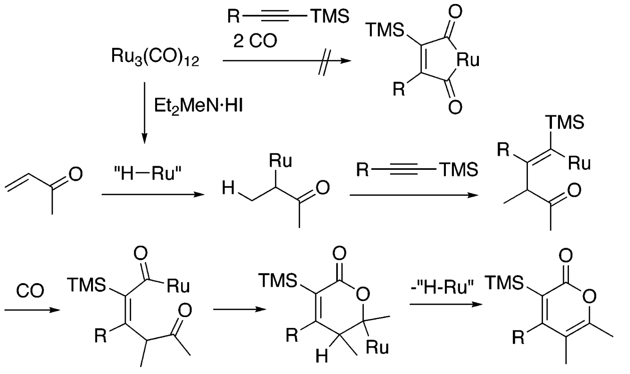
[7] Hua, R.; Tanaka, M. *New J. Chem.* **2001**, *25*, 179.

to a slight improvement in the yield of **3a** (entry 3). The addition of $Et_2MeN{\cdot}HI$ gave an increased yield of **3a** (40% yield). In this reaction, a four-component coupling product **4a**, in which two molecules of methyl vinyl ketone had been incorporated, was also formed as a byproduct in 15% yield (entry 5). The slight modification of the reaction conditions (higher temperature, smaller amounts of **2a**, and shorter reaction time) gave a better yield of **3a** (52%) and a reduced yield of **4a** (7%) (entry 6). Although $[RuCl_2(CO)_3]_2$ also exhibited catalytic activity, other ruthenium complexes and other metal carbonyl complexes, such as $RuHCl(PPh_3)_3$, $[Cp^*RuCl_2]_2$, $CpRuCl(PPh_3)_2$, $[RuCl_2(\eta^6\text{-mesitylene})]_2$, $Rh_6(CO)_{16}$, and $Ir_4(CO)_{12}$, were not effective for the present pyrone formation.

Using $Ru_3(CO)_{12}$ as a catalyst and $Et_2MeN{\cdot}HI$ as an additive, the cycloaddition of several silylacetylenes and alkenes was carried out, and the results are shown in Table 2. The reaction of ethyl vinyl ketone **2b** and octyl vinyl ketone **2c** with **1a** and CO gave the corresponding α-pyrones **3b** and **3c** in 57 and 55% yields, respectively (entries 2 and 3). The reaction of cyclohexenone (**2d**) also proceeded, giving the bicyclic α-pyrone **3d** in 37% yield (entry 4).[8] Aliphatic silylacetylene such as 1-(trimethylsilyl)-1-octyne (**1b**) gave the corresponding α-pyrone **3e** in low yield (entry 5). A variety of aryl-substituted silylacetylenes **1c−g** were examined, all of which gave the corresponding α-pyrones **3f−j** in good to moderate yields (entries 6−10). Triethylsilyl- and tigermyl-substituted acetylene **1h** and **1i** gave the corresponding α-pyrones **3k** and **3l** in low yields (entries 11 and 12).

A possible mechanism for the present cycloaddition reaction is shown in Scheme 2. A ruthenium hydride species, generated from the ruthenium carbonyl complex with an amine·HI salt or water,[9] would react with methyl vinyl ketone (**2a**) to give a ruthenium enolate.[10] Carboruthenation of the enolate to silylacetylene gives a vinyl ruthenium complex, which then undergoes CO insertion to give an acyl ruthenium complex. Cyclization, followed by β-hydride elimination would give the α-pyrone and regenerate the ruthenium hydride species. In our previous work on hydroquinone synthesis by ruthenium-catalyzed [2+2+1+1] cycloaddition, we proposed that the maleoylruthenium complex, which arises from the reaction of ruthenium with one molecule of alkyne and two molecules of carbon monoxide, could serve as key intermediate.[5] In the present case, the formation of maleoylruthenium would be suppressed by the trimethylsilyl substituent of the alkyne, but the precise reason for this is not clear at the present stage.

Scheme 2. Possible Reaction Mechanism



In summary, we report a novel ruthenium-catalyzed [3+2+1] cycloaddition reaction leading to tetrasubstituted α-pyrones, which uses silylacetylenes, α,β-unsaturated ketones, and CO as the starting materials. A further extension of the present cycloaddition reaction as well as detailed mechanistic studies are currently ongoing in our laboratory.

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Supporting Information Available: Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Acrolein can participate in the cycloaddition leading to α-pyrone in low yield (9%), whereas ethyl acrylate failed to react with **1a** and CO.

(9) Torii, S.; Okumoto, H.; Sadakane, M.; Xu, L. H. *Chem. Lett.* **1991**, 1673.

(10) For examples of catalytic transformations containing ruthenium enolates: (a) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436. (b) Uma, R.; Davies, M.; Crévisy, C.; Grée, R. *Tetrahedron Lett.* **2001**, *42*, 3069. (c) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2000**, *122*, 8081. (d) Chang, S.; Na, Y.; Choi, E.; Kim, S. *Org. Lett.* **2001**, *3*, 2089. (e) Wang, H.; Watanabe, M.; Ikariya, T. *Tetrahedron Lett.* **2005**, *46*, 963. (f) Doi, T.; Fukuyama, T.; Minamino, S.; Husson, G.; Ryu, I. *Chem. Commun.* **2006**, 1875. (g) Doi, T.; Fukuyama, T.; Horiguchi, J.; Okamura, T.; Ryu, I. *Synlett* **2006**, 721.